VERIFICATION OF TRANSLATION

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declare as follows:

1. That I am well acquainted with both the English and German languages, and

2. That the attached document is a true and correct translation to the best of my knowledge and belief of:

   Priority document of the German patent application 102 15 067.2

Munich, 24 January 2007
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(Date)

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(Dirk Bühler)

(No witness required)

PHARMACEUTICAL PREPARATION THAT IS STABLE IN STORAGE AND CONTAINS OXYCODONE AND NALOXONE

The invention relates to a pharmaceutical preparation that is stable in storage and contains oxycodone and naloxone.

Treatment of severe pain occurring as a result of diseases such as cancer, rheumatism and arthritis takes a central position in the treatment of these diseases. The scope of pain perceived by tumor patients includes periosteal pain and bone pain, visceral pain and soft tissue pain, but all these forms of pain make the daily life of the patients intolerable and often lead to depressive states. Successful pain therapy which permanently improves the patient's quality of life is therefore at least as important for the success of a comprehensive therapy as is the treatment of the actual causes of the disease.

Because of the importance of successful pain therapy, the World Health Organization (WHO) has developed a four-step model for treatment of patients with tumor pain; this model has proven suitable in everyday practice. This model can also be applied to patients with chronic pain or pain resulting from diseases other than cancer. Depending on the intensity, quality and location of the pain, four stages of treatment are differentiated, but in all cases the next higher stage is indicated when the effect of the analgesic used up to that point is no longer sufficient (Ebell, H. J.; Bayer, A. (eds.): Treatment of pain in tumor patients, Thieme, 1994 (Supportive Measures in Oncology, Vol. 3) and Zech, D.; Grond, S.; Lynch, J.; Hertel, D.; Lehmann, K.: Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study, Pain (1995), 63, 65-76).

According to this stage model from the WHO, the opioid analgesics play a central role in treatment of pain. In addition to morphine, which represents the prototype of these active ingredients, the opioid analgesic group also includes oxycodone, hydromorphone, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives thereof, methadone, dextropropoxyphene, buprenorphine, pentazocine, tilidine, tramadol and hydrocodone. The ATC classification (Anatomical Therapeutic Chemical classification) of the WHO indicates whether an active ingredient is classified as an opioid analgesic. The pronounced pain-relieving effect of the opioid analgesics is based on the fact that they simulate the effect

of endogenous morphine-like substances (endogenous opioids) whose physiological function consists of controlling the perception and processing of pain stimuli.

Opioids suppress the conduction of pain stimuli, whereby in addition to directly inhibiting neural stimulus transmission in the spinal cord induced directly by the action of opioids, activation of nerve pathways is also important, these pathways leading from the brain stem into the spinal cord where they inhibit pain conduction. In addition, opioids suppress the perception of pain in the thalamus and also influence the affective assessment of pain by acting in the limbic system.

Opioid receptors occur in various locations in the body. The receptors in the intestinal area on the one hand and in the brain on the other hand are especially important for pain therapy with opioids, in particular because of the different adverse effects of having these different receptors occupied.

Opioid analgesics are known as strong agonists when they bind with a high affinity to the opioid receptors and trigger a marked inhibition of the perception of pain. Substances that also bind with a high affinity to opioid receptors but do not cause the perception of pain to be lowered and therefore counteract the opioid agonists are known as antagonists. Depending on the binding behavior and activity induced, it is therefore possible to differentiate pure agonists, mixed agonists/antagonists and pure antagonists among the opioids. The antagonists include, for example, naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxonazine, methylnaltrexone, ketyl-cyclazocine, norbinaltorphimine, naltrindole, 6-β-naloxol and 6-β-naltrexol (W. Forth, D. Henschler, W. Rummel, K. Starke: Allgemeine und Spezielle Pharmakologie und Toxikologie [General and Specific Pharmacology and Toxicology], 7th edition, 1996, Spektrum Akademischer Verlag, Heidelberg, Berlin, Oxford).

On the basis of their good analgesic efficacy, substances such as oxycodone, tilidine, buprenorphine and pentazocine in the form of pharmaceutical drugs have gained acceptance in pain therapy. Medications such as Oxigesic® (with oxycodone as the analgesic component) and Valoron® (with tilidine as the analgesic component) have proven successful in pain therapy.

However, the use of opioid analgesics in pain therapy may be associated with some negative adverse effects. Long-term use of opioid analgesics can lead to physical and psychological dependency.

In pain patients in particular, physical dependency results in progressively higher doses of the analgesic being required after prolonged use (so-called development of tolerance). The euphoric effect of opioid analgesics results in frequent abuse of these analgesics. Drug abuse and psychological dependency occur especially in juveniles. These dangerous effects ranging from unwanted habituation to fully developed addiction are caused in particular by the strong action of the substances which are used in medicine for fully legitimate purposes and cannot be dispensed with.

When using effective opioid analgesics in pain therapy, there are often adverse effects in addition to the aforementioned disadvantages, e.g., constipation, respiration depression, nausea and sedation. Less commonly difficulties in urination and urine retention may occur. Various attempts have been made to counteract the habituation processes and adverse effects that occur in pain therapy. For example, traditional treatment methods may be relied on, involving mainly drug withdrawal measures in the event of development of a dependency or administration of laxatives in the case of constipation.

Other procedures, however, are aimed at canceling the addictive and habituating potential and/or the adverse effects of opioid analgesics by administering an antagonist that counteracts the opioid analgesic. These antagonists include naltrexone and naloxone.

In particular there has been no lack of proposals of a technical type for how to use these active ingredients to prevent unwanted habituation and dependency or even the signs of addition.

United States Patent 3,773,955 and United States Patent 3,966,940 have proposed formulating analgesics in combination with naloxone to prevent dependency-inducing effects such as euphoria and the like with parenteral administration. Avoidance of the adverse effects such as constipation is not even mentioned there.

To restrict parenteral abuse of oral dosage forms, US Patent 4,457,933 proposes a combination of morphine with naloxone in defined ranges. This document also fails to mention preventing adverse effects such as constipation.

Again for the purpose of preventing abuse, United States Patent 4,582,835 describes a combination preparation consisting of buprenorphine and naloxone to be administered parenterally or sublingually.

European Patent Application EP 0 352 361 A1 relates to the treatment of constipation in pain therapy by oral administration of an opioid analgesic and an antagonist, whereby prodrug forms of the antagonist naltrexone and naloxone are used. However, this patent application does not relate to preventing abuse of the opioid analgesic.

German Patent Application DE 43 25 465 A1 also relates to the treatment of constipation during pain therapy by a preparation consisting of an opioid agonist and an antagonist. The characteristic feature of this known teaching is that the antagonist, which is naloxone, must be present in larger amounts than the opioid agonist, which is preferably morphine, and must not have a delayed release. This should ensure that the antagonist can manifest its constipation-preventing effect without diminishing the analgesic effect of the agonist. However, this patent application does not relate to preventing abuse of an opioid analgesic.

To prevent adverse effects such as constipation and respiratory depression during pain therapy, combination preparations that are taken orally and consist of an opioid analgesic plus the opioid antagonist naloxone have been brought on the market. The preparation Talwin® from the company Windrop/Sterling contains pentazocin and naloxone. The preparation Valoron® from the company Goedeke is a tilidine-naloxone combination.

In addition to a good analgesic effect and reducing the addiction potential as well as preventing adverse effects, medications suitable for successful pain therapy should have other properties.

Pharmaceutical drugs must be formulated in general so that the active ingredients remain stable for the longest possible period of time under standard storage conditions and the intended release profiles of the active ingredients do not change even after a prolonged storage time.

In addition, it should be possible (even with agonist/antagonist combinations) to select the release profile of the individual active ingredient as needed. The measures to be taken should not make it difficult or even prevent the release profile of other active

ingredients (e.g., in active ingredient combinations) from being selected as needed. Thus there should not be any mutual dependence of the release rate of the substances.

Medications for pain therapy should either have such high active ingredient contents or should be formulated so that they need only be taken rarely by the patient. The simpler the dosage regimen for the analgesic and the easier it is for the patient to understand why he must take certain tablets and how often, the better patient compliance will be in following the physician's instructions. A low need for taking an analgesic ensures a high stability in taking the analgesic (compliance) on the part of the patient.

By using so-called sustained-release formulations, i.e., drug formulations from which the active ingredients are released with a sustained effect over a longer period of time, attempts have been made to reduce the frequency with which therapeutic pain drugs must be taken and therefore increase patient compliance. Such sustained-release formulations also appear appropriate from the standpoint that the dependency-causing potential of this active ingredient is reduced by the delayed release of an opioid analgesic.

This is based on the fact that the addictive potential of an active ingredient is defined not by the active ingredient per se but instead by the method of administration and the associated pharmacodynamics. In addition to the essentially psychotropic effects of an opioid, the speed with which the brain is flooded is a more important criterion for the risk of dependency than the active ingredient per se (Nolte, T.: STK – Zeitschrift für angewandte Schmerztherapie [Journal for Applied Pain Therapy], 2001, Vol. 2).

The analgesic Oxigesic® from Purdue is a preparation from which the opioid analgesic oxycodone is released with a sustained effect. Despite the lower need for taking the medication achieved through this formulation and the reduced addiction potential, the adverse effects as such still exist and the risk of developing an addiction cannot be ruled out because Oxigesic® does not contain any opioid antagonist.

According to the above-mentioned European Patent Application EP 0 352 361 A1, neither the opioid analgesic nor the antagonist is formulated for delayed release. Accordingly, the duration of effect of such preparations is limited, they must be taken several times a day and the desired patient compliance is not ensured. This patent application does not disclose either the advantages or formulations of preparations characterized by stable and independent release of the active ingredient components

over a period of time. The stability of such preparations in storage is also not the subject of this patent disclosure.

German Patent Application DE 43 25 465 A1 discloses formulations according to which the constipation that occurs during pain therapy is to be prevented by the fact that although the opioid agonist is released with a sustained effect, the antagonist which is present in excess must not be released with a sustained effect. Owing to the high first pass effect of naloxone, comparatively large amounts of this active ingredient must therefore be used. This patent application does not disclose either the advantages or formulations of preparations characterized by a stable and independent release of the active ingredient components over time nor is the stability of such preparations in storage the subject matter of the disclosure content of this patent. With the corresponding preparations, the treating physician must therefore perform complex titration experiments each time the dosage is increased.

The company Goedeke has brought on the market under the brand name Valoron® an analgesic which is a combination of tilidine plus naloxone. According to company reports, this is a formulation from which both active ingredient components are release with a sustained effect. The matrix required for this has a relevant amount of water-swellable material (HPMC) and can therefore be regarded as a swellable (and possibly partially eroding) diffusion matrix. A disadvantage of this known formulation is that tilidine and naloxone have different release profiles under the same conditions but with different absolute quantities when the release is measured at certain pH levels. The release rates of the agonist and antagonist are not independent of one another, which is seemingly due to the sustained-release formulation used. It is thus necessary for a treating physician to conduct complex titration experiments for each individual patient whenever an increase in dosage is desired, despite the identical tilidine/naloxone ratio, because it cannot be assumed that the release behavior of the two active ingredients remains in principle constant. The spectrum of therapeutic amounts of the analgesic available for the treating physician is thus limited.

The objects of the present invention include in particular making available a pharmaceutical preparation for pain therapy which has a reduced abuse potential and reduced adverse effects with a high analgesic effect, while being characterized by a reduced need for taking the medication and therefore increased compliance as well as the possibility of individualizing the dosage for each patient. Another object of the present invention is to make available formulations for pharmaceutical preparations for

pain therapy that ensure that the active ingredients of the preparations remain stable for a long period of time in storage and the release of the active ingredients remains the same reproducibly even after a long period of storage and the active ingredients are released independently of one another.

The features of the independent patent claim serve to achieve this object as well as additional objects derived from the description of the present invention. Advantageous embodiments of the present invention are defined in the subclaims.

The objects are achieved according to the present invention by the fact that a preparation that contains oxycodone and naloxone and is stable in storage and is formulated so that these active ingredients are released from the preparation in a sustained, invariant and independently manner.

By combining oxycodone (in an analgesically effective amount) and naloxone, this ensures that the inventive preparations will have an effective analgesic action while the usual adverse effects such as constipation, respiratory depression and development of addiction are suppressed or greatly reduced. A matrix formulation that remains stable for long periods of time ensures that the agonist and antagonist will always be released in predetermined percentage amounts without mutually influencing the rates of release. This prevents abuse of the medication, which presupposes that oxycodone can be selectively extracted from the formulation. With the inventive formulation, regardless of the absolute and relative amounts of agonist and antagonist, it is impossible to separate the agonist from the preparation without the corresponding antagonist component.

In addition, the inventive formulation of a pharmaceutical drug ensures that the active ingredients in particular will manifest the same release behavior with the same quantity ratios regardless of the absolute amount present. Such an independent release behavior provides the physicians with a broad spectrum of absolute quantities of analgesic substance that can be used with known optimal agonist/antagonist ratios. This allows convenient, individualized adjustment of the dose for the particular patient and a stepwise increase in dose as well as, if necessary, a stepwise reduction in dose. This individualized dosage is extremely relevant for medical reasons.

The characterizing features of the present invention, namely the delayed, invariant and independent release of the active ingredient components, also ensure that the pharmaceutical preparations produced according to this invention are characterized in

that they need not be taken often, which results in high compliance. Furthermore, the inventive preparations allow an individualized dosing for each patient on the part of the physician. The inventive preparations allow use over a broad range with regard to the absolute quantities of active ingredients that may be used and ensure that the active ingredients are in a stable form even after a prolonged storage time and are active with the same release profiles.

Within the context of the present invention, the term "delayed release" (and/or sustained release) of active ingredients is understood to mean that the pharmaceutically active ingredients are released from a pharmaceutical drug over a longer period of time than is the case with the known formulations for immediate release. Release over a period of 2 to 20 hours, especially preferably for 2 to 16 hours or 2 to 12 hours is preferred, whereby the specifications must comply with statutory standards.

Drug formulations that ensure such a delayed release of the active ingredients from the pharmaceutical drug preparation are referred to within the context of the present invention as sustained formulations or prolonged release formulations. The term "prolonged release" as used according to this invention does not mean that the active ingredients are released from the drug formulation as a function of pH. Instead, release of the active ingredients from the inventive formulations is independent of pH. The term "prolonged release" is used according to this invention instead refers to the release of the active ingredients of a pharmaceutical drug over a longer period of time. It does not refer to controlled release at a defined location, i.e., so that the active ingredients are released either specifically only in the stomach or only in the intestinal area. (Of course such a local release could additionally be achieved in the individual case, e.g., by enteric coating of the pharmaceutical drug. According to current information, however, this does not appear to be advantageous as a rule.)

The term "independent release" is understood according to this invention to mean that in the presence of at least two active ingredient components, the change in the absolute amount of one component does not have any effect on the release profiles of the other components and this does not change. Such an independent release behavior is independent of the pH at which the release is measured in the inventive formulations or it is obtained independently of the type of production process for the formulation. In particular, the pH independence in an acidic range, i.e., at a pH < 7. The release profile (and/or behavior) is understood to refer to the release of active ingredients from the

formulation over a period of time in percentage of the absolute amount of this active ingredient as determined with conventional tests.

In concrete terms, this means, for example, that the release profile of oxycodone, as observed in an oxycodone/naloxone combination with 12 milligrams oxycodone and 4 milligrams naloxone does not change when a corresponding preparation contains 12 milligrams oxycodone but 6 milligrams naloxone in an identical formulation.

The terms "invariant release behavior" and/or "release profile" are understood according to this invention to mean that the percentage amount of the absolute content amount of each active ingredient released per unit of time does not change significantly and remains sufficiently constant if the absolute amounts are changed. Sufficiently constant percentage amounts are understood to refer to the fact that the percentage amount of pharmaceutical drug release per unit of time fluctuates about a mean value by no more than 20%, preferably no more than 15% and especially preferably by no more than 10%. The mean value is determined from measurements of six release profiles. The quantity of substance released per unit of time must of course fulfill the specifications as stipulated by lawmakers.

In concrete terms, this means that with an oxycodone/naloxone combination of 12 mg oxycodone and 4 mg naloxone, for example, 25% oxycodone and 20% naloxone are released within the first 4 hours and with an oxycodone/naloxone combination of 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 20% naloxone are released within the first 4 hours, and in both cases the deviation is no greater than 20% based on the mean value (in this case 25% oxycodone and/or 20% naloxone).

The term "storage stable" as used according to this invention is understood to mean that after storage under standard conditions (at least 2 years at room temperature and conventional humidity), the active ingredient contents of a pharmaceutical drug formulation do not differ from the initial contents by more than the values stipulated in the specifications and/or pharmacopoeias. The term "stable in storage" is also to be understood according to the present invention as meaning that under standard conditions (60% relative humidity, 25°C) a preparation produced according to the present invention is stable in storage in a manner that conforms to the approval specifications.

The terms "storage stable" and/or "stable over time" as used according to this invention are also to be understood as meaning that active ingredient components have a release

profile like that manifested with immediate use without storage even after a prolonged storage time under standard conditions. The allowed fluctuations with regard to the release behavior are characterized according to this invention in that the quantity of substance released per unit of time must not fluctuate by more than 20%, preferably by no more than 15% and especially preferably by no more than 10% with regard to a mean value. The mean value is determined by measuring six release profiles.

The release of active ingredients from a sustained-release formulation is measured by means of HPLC using the basket method according to the USP at pH 1.2 or pH 6.5.

To determine the stability in storage, the corresponding release rates are measured by means of HPLC using the basket method according to the USP at pH 1.2.

Within the context of the present invention, the terms "agonist" and "analgesic" are always understood to refer to oxycodone. The term "antagonist" is always understood to refer to naloxone within the context of the present invention.

The preparations produced according to this invention may be administered orally, nasally, rectally and/or by inhalation for use in pain therapy. Parenteral administration is not intended according to the present invention. Formulation of the medication for oral administration is especially preferred.

Although not stated explicitly, the term agonist or antagonist always refers to derivatives, salts and the like that may be used pharmaceutically and have the same effect. When referring here to oxycodone or naloxone, this includes in addition to the base, their hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate, succinate and the like.

According to this invention, the agonist and antagonist are formulated to be released from the resulting pharmaceutical preparations independently and invariantly and with a sustained effect. This does not mean that the antagonist is present in excess in relation to the agonist. Instead it is preferable for the agonist to be present in excess in relation to the antagonist in formulations of agonist/antagonist combinations having the inventive release profile.

The excess of the agonist is to be based here on the unit dose amount of the antagonist present in the combination preparation. The excess of opioid agonist is usually indicated by giving the weight ratios of agonists to antagonists.

Preferred weight ratios of oxycodone to naloxone are in the weight ratio range from max. 25:100, especially preferably in the weight ratio ranges of 15:1, 10:1, 5:1, 4:1, 3:1, 2:1 or 1:1.

The absolute quantities of agonist and antagonist to be used depend on the particular active ingredients. According to this invention it is important to be sure that the agonist and antagonist are released from a pharmaceutical preparation formulated for delayed release only in an independent and uniform manner.

With an inventive combination preparation of oxycodone and naloxone, preferably between 10 mg and 150 mg, especially preferably between 10 mg and 80 mg of oxycodone is used (commercial strength) and preferably between 1 mg and 50 mg naloxone is used per unit dose.

According to this invention, the ratio between oxycodone and naloxone is to be selected so that the inventive release behavior of both active ingredients is ensured and the agonist manifests an analgesic effect while the antagonist content is selected so that the addictive effects or addiction-inducing effects and/or the adverse effects of the agonist are reduced or eliminated without any effect on the analgesic action of the agonist. Adverse effects of analgesic opioid agonists are understood according to this invention to refer to the addictive and habituation effects as well as constipation and respiratory depression.

According to this invention, conventional formulations may be used in general if the ensure that the active ingredients in the preparation are released with a time delay, independently and uniformly. The formulations are to be selected according to this invention so that the active ingredients are stable in storage.

Preferably matrix-based sustained-release formulations are suitable for the inventive release of agonist and antagonist. Formulations with a nonswelling diffusion matrix are especially preferred according to this invention. At the present time, formulations with an erosion matrix or a swelling diffusion matrix are not preferred.

According to this invention, the matrix which ensures delayed release of the active ingredients is to be selected so that the release of the active ingredients is delayed, independent and invariant. Such matrices preferably include polymers based on ethylcellulose. Ethylcellulose is especially preferred. Matrices using such polymers as those available commercially under the brand name Surelease® E-7-7050 are especially preferred.

Formulations with an inventive release behavior include in particular matrices containing ethylcellulose as the component having an essential influence on the release properties of the matrix and also containing at least one fatty alcohol.

Matrices based on polymethacrylate (e.g., Eudragit® RS30D and Eudragit® RL30D) or those containing relevant amounts of water-swellable material, in particular hydroxyalkyl celluloses such as HPMC will not be used according to this invention based on the information currently available.

It is thus possible to produce preparations which release the active ingredients with a sustained effect, independently and uniformly and in equal amounts per unit of time can thus also be produced with the matrices according to this invention. In concrete terms, this means that with an oxycodone/naloxone combination of 12 mg oxycodone and 4 mg naloxone, for example, 25% oxycodone and 25% naloxone will be released within the first 4 hours, and with an oxycodone/naloxone combination of 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 25% naloxone will be released within the first 4 hours, whereby in both cases the deviation is no greater than 20%, based on the mean value (in this case 25% oxycodone and/or naloxone).

Such identical release behavior of the two active ingredients may be desirable under certain medical conditions.

According to this invention, formulations that ensure the inventive release of the active ingredient components may also contain, in addition to the matrix-forming polymers, fillers and excipients such as granulation aids, lubricants, internal lubricants, coloring agents and flow agents as well as plasticizers.

Fillers that may be used include sugars such as lactose, glucose or sucrose, starches and their hydrolysates, microcrystalline cellulose, cellactose, sugar alcohols such as sorbitol

or mannitol, sparingly soluble calcium salts such as calcium hydrogen phosphate, dicalcium or tricalcium phosphate.

Povidone, for example, may be used as a granulation aid.

Preferably highly dispersed silica (Acrosil®), talc, cornstarch, magnesium oxide, magnesium or calcium stearate may be used as the flow agents or lubricants.

Suitable internal lubricants include preferably magnesium stearate and/or calcium stearate. Likewise, fatty acids such as stearic acid or fats such as hydrogenated castor oil may preferably also be used.

Likewise polyethylene glycols and fatty alcohols, e.g., cetyl and/or stearyl alcohol and/or cetostearyl alcohol may be used as excipients that are used for the sustained-release effect.

When using filers and excipients such as coloring agents and the aforementioned lubricants and flow agents as well as plasticizers, it is important to be sure that only such combinations that ensure the inventive release properties for the active ingredients can be used according to this invention together with the matrix-forming substance and/or the matrix-forming substances.

All these additional formulation ingredients are preferably selected so that the release matrix has the character of a diffusion matrix that is essentially nonswelling and noneroding in water and/or in buffer solution.

According to this invention, a formulation containing ethylcellulose or Surelease® E-7-7050 as the matrix-forming substance, containing stearyl alcohol as the fatty alcohol, containing magnesium stearate as the flow agent and containing lactose as the filler and povidone as the granulation agent is especially preferred according to this invention.

The inventive preparations may be produced in any conventional dosage form that is fundamentally suitable for sustained formulations and ensures that the active ingredients will be released in the manner according to this invention. In particular, tablets are suitable, including multilayer tablets and capsules. In addition, however, dosage forms such as granules or powders may also be used, but only those dosage forms which have an adequate delayed release and inventive release behavior are allowed.

The inventive pharmaceutical preparations or precursors thereof can be synthesized buildup and/or breakdown granulation. Spray granulation with subsequent drying of the granules is preferred. Buildup granulation in a drum or on a granulation disk is also preferred. The granules can then be pressed to form tablets, for example, by using suitable excipients.

It is especially advantageous to produce the inventive pharmaceutical preparations or precursors thereof by extrusion. Melt extrusion with a co-current or countercurrent twin-screw extruder is preferred. Extrusion methods using single-screw and/or multi-screw extruders are also preferred.

Examples representing particularly preferred embodiments of the present invention are presented below. In addition, examples which illustrate the advantages of inventive preparations in comparison with traditional formulations are also presented. These examples are not to be interpreted as being restrictive in any sense.

Example 1 – Production of tablets with different amounts of oxycodone/naloxone with a nonswelling diffusion matrix by spray granulation:

The following amounts of the components listed were used for inventive production of oxycodone/naloxone tablets:

Preparation (name)	Oxy/Nal-0	Oxy/Nal-5	Oxy/Nal-10
Oxycodone HCl	20.0 mg	20.0 mg	20.0 mg
Naloxone HCl	-	5.0 mg	10.0 mg
Lactose Flow Lac 100	59.25 mg	54.25 mg	59.25 mg
Povidone 30	5.0 mg	5.0 mg	5.0 mg
Surelease	10.0 mg solids	10.0 mg solids	10.0 mg solids
Stearyl alcohol	25.0 mg	25.0 mg	25.0 mg
Talc	2.5 mg	2.5 mg	2.5 mg
Mg stearate	1.25 mg	1.25 mg	1.25 mg

The Surelease® E-7-7050 polymer mixture used had the following composition:

Surelease® E-7-7050
Ethylcellulose 20 cps
Dibutyl sebacate
Ammonium hydroxide
Oleic acid
Silicon dioxide
Water

Oxycodone HCl, naloxone HCl, povidone 30 and Lactose Flow Lac 100 were mixed in a free-fall mixer (Bohle) and then spray-granulated with Surelease® E-7-7050 in a fluidized bed granulator (GPCG3) to produce the tablets. The material was then passed through a Comill 1.4 mm screen. In addition, a granulation step was performed using molten fatty alcohol in a forced mixer (Collette Gral). All the tablet cores produced in this way have a weight of 123 mg, based on the dry substance.

Example 2 – Production of tablets with oxycodone and naloxone in a nonswelling diffusion matrix by extrusion:

The following amounts of the components indicated were used for the inventive production of oxycodone/naloxone tablets by extrusion:

Preparation (name)	Oxy/Nal-Extr
Oxycodone HCl	10 mg
Naloxone HCl	10 mg
Collidone 30	6 mg
Lactose Flow Lac 100	49.25 mg
Ethylcellulose 45 cpi	10 mg
Stearyl alcohol	24 mg
Talc	2.5 mg
Mg stearate	1.25 mg

The stated amounts of oxycodone HCl, naloxone HCl, ethylcellulose 45 cpi, Collidone 30, Lanette 18 and Lactose Flow Lac 100 were weighed into a Bowle free-fall mixer and mixed there. Then this mixture was extruded through a contra-rotating twin-screw extruder of the type Micro 18 GGL from the company Leistritz AG, Nuremberg. The

temperature of heating zone 1 was 25°C, that of heating zone 2 was 50°C, that of heating zones 3 through 5 was 60°C, that of heating zones 6 through 8 was 55°C, that of heating zone 9 was 60°C and that of heating zone 10 was 65°C. The worm gear speed was 150 rpm, the resulting melt temperature was 87°C, the feed rate was 1.5 kg/h and the diameter of the nozzle opening was 3 mm. The extruded material was passed through a Frewitt 0.68 × 1.00 mm screen. This milled extrudate was mixed with talc and magnesium stearate, passed through a 1 mm hand screen and pressed to form tablets. The extruder had a screw geometry like that illustrated in Figure 1.

In comparison with the production of oxycodone/naloxone tablets likewise having a nonswelling diffusion matrix based on Surelease® by spray granulation (see Example 1), the extruded preparation contains fewer components in the product.

Example 3 – Release behavior of oxycodone/naloxone tablets from Example 1:

Release of the active ingredients was investigated by means of HPLC over a period of 12 hours using various tablets Ox/Nal-0, Ox/Nal-5 and/or Ox/Nal-10 according to the basket method as described in USP at pH 1.2.

Figure 2 and the values given in the table show that in the case of a nonswelling diffusion matrix based on Surelease®, the release of oxycodone remains the same regardless of the amount of naloxone. Likewise, uniform release profiles are obtained from naloxone with different amounts of oxycodone.

Time (min)	Ox/Nal-0	Ox/Nal-5-O	Ox/Nal-5-N	Ox/Nal-10-O	Ox/Nal-10-N
	Oxy	Oxy	Nal	Oxy	Nal
0	0	0	0	0	0
15	26.1	24.9	23.5	22.8	24.1
120	62.1	63	61	57.5	60.2
420	91.7	94.5	91.9	89.4	93.5
720	98.1	99.6	96.6	95.7	100.6

The release values are based on oxycodone or naloxone (line 2) and are given in percentage amounts. The mean value of the release of naloxone, for example, is 92.7% at 420 minutes. The maximum deviation at this measurement point in time is 1%. "Oxy"

and "Nal" stand for oxycodone and naloxone, respectively, and indicate the particular active ingredient being investigated.

Example 4 – Release behavior of oxycodone/naloxone tablets from Example 2 at various pH levels:

The release of the active ingredients from the tablets was investigated by means of HPLC over a period of 12 hours at pH 1.2 and for a period of 1 hour at pH 1.2 and then for 11 hours at pH 6.5, using the basket method according to USP.

The following release rates were obtained at 12 hours and pH 1.2:

Time (min)	Oxy/Nal-Extr-1.2-O	Oxy/Nal-Extr-1.2-N
	Oxy	Nal
0	0	0
15	24.1	24.0
120	62.9	63.5
420	92.9	93.9
720	96.9	98.1

The following release rates were obtained at 1 hour and pH 1.2 and 11 hours and pH 6.5:

Time (min)	Oxy/Nal-Extr-6.5-O	Oxy/Nal-Extr-6.5-N
	Oxy	Nal
0	0	0
60	48.1	49.2
120	65.0	64.7
240	83.3	81.8
420	94.1	92.3

The release values are based on oxycodone or naloxone (line 2) and are given in percentage amounts. "Oxy" and "Nal" stand for oxycodone and naloxone, respectively, and indicate the particular active ingredient being investigated.

First, it is clear from a comparison of the values given in the tables of Example 4 and the table of Example 3 that regardless of the production process, the active ingredients are released from the preparations in uniform amounts. For example, after 420 minutes, 89.4% of oxycodone has been released from spray granulated tablets (Ox/Nal-10 tablets, see Example 3) and after 420 minutes, 92.9% has been released from the extruded tablets (Oxy/Nal-Extr 1.2-O, Example 4). The deviation in the release of oxycodone from extruded tablets thus differs by 1.1% from the mean value of the release of oxycodone from spray-granulated tablets (91.9% at 420 minutes). At 420 minutes, 93.5% naloxone has been released from spray granulated tablets (Ox/Nal-10 tablets, see Example 3) and after 420 minutes, 93.9% naloxone has been released from extruded tablets (Oxy/Nal-Extr 1.2-O, Example 4). The deviation in the release of naloxone from extruded tablets thus differs by 1.3% from the mean value of the release of naloxone from spray-granulated tablets (92.7% at 420 min).

In addition, a comparison of the values given in the tables of Example 4 and Figures 3A and 3B reveals that regardless of the pH at which the measurement of the release rates is performed, the release of oxycodone and naloxone likewise remains the same.

Example 5 – Comparative example: Release behavior of Valoron® tablets:

Release of the active ingredients from the tablets was investigated by means of HPLC for 1 hour at pH 1.2 and in 6 hours at pH 6.5 using the basket method according to USP.

It can be seen from Figures 4A and 4B and the values given in the table that in the case of a swelling diffusion matrix (and possibly also eroding) with relevant amounts of HPMC, the release of various amounts of tilidine with different amount of naloxone varies significantly and is not uniform. This is also true of naloxone converse. This means that at this pH the active ingredients are not released in an independent manner.

Time (min)	Ti/Nal-50/4-T	Ti/Nal-50/4-N	Ti/Nal-100/8-T	Ti/Nal-100/8-N	Ti/Nal-150/12-T	Ti/Nal-150/12-N
	Til	Nal	Til	Nal	Til	Nal
0	0	0	0	0	0	0
60	37.2	27.6	33.9	27.3	29.9	23.3
120	47.6	31.7	46.5	33.4	41.5	28.5
180	54.7	37.4	55	41.2	48.2	35
240	59.7	44	68.2	59.5	54.5	40.1
300	65.2	50.6	82.6	72.9	60.5	47.5
360	70.3	58	85.7	82.7	67.2	56.4
420	74.2	60.8	93.1	90.9	84.9	78.9

The release values are based on tilidine or naloxone (line 2) and are given in percentage amounts. The mean value of the release of naloxone is 78.87% after 420 minutes, for example. The maximum deviation at this measurement point in time is 20.4%. "Til" and "Nal" stand for tilidine and naloxone, respectively, and indicate the particular active ingredient investigated in each case.

Example 6 – Electron microscopic comparison of the structure of tablets from Example 1 and Example 2 with Valoron® N tablets

For the electron microscopic analysis, the tablets used included tablets containing 20 mg oxycodone and 10 mg naloxone, produced either by spray granulation according to Example 1 (Ox/Nal-10) or by extrusion according to Example 2 (Oxy/Nal-Extr) and a Valoron® N tablet with 100 mg tilidine and 8 mg naloxone.

Figures 5A and 5B show different enlargements of scanning electron micrographs of an Ox/Nal-10 tablet with the inventive formulation produced by spray granulation. Figures 6A and 6B show different enlargements of scanning electron micrographs of an Oxy/Nal-Extr tablet with the inventive formulation produced by extrusion. Figures 7A and 7B show scanning electron micrographs of the Valoron® N tablet.

It can be seen clearly from a comparison of these figures that tablets with an inventive formulation have a much finger and more homogeneously structured surface with fewer cracks than the Valoron tablet regardless of whether they are produced by spray

granulation or by extrusion. This structural difference may be the reason for the difference in the release behavior of the preparations used.

CLAIMS

1. A storage stable pharmaceutical preparation comprising oxycodone and naloxone, characterized in that the active ingredients are released from the preparation in a sustained, invariant and independent manner.

2. The preparation according to Claim 1, characterized in that oxycodone and/or naloxone is present in the form of its pharmaceutically acceptable and equally active derivatives thereof such as the base, salts and the like.

3. The preparation according to Claim 2, characterized in that oxycodone and/or naloxone is in the form of the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

4. The preparation according to any one of the preceding claims, characterized in that oxycodone is present in excess, based on the unit amount of naloxone.

5. The preparation according to any one of the preceding claims, characterized in that naloxone is present in a quantity range from 1 mg to 50 mg.

6. The preparation according to any one of the preceding claims, characterized in that oxycodone is present in a quantity range from 10 mg to 150 mg, preferably 10 mg to 80 mg.

7. The preparation according to any one of the preceding claims, characterized in that it contains oxycodone and naloxone in a weight ratio range from max. 25:1, preferably max. 20:1, 15:1, especially preferably 5:1, 4:1, 3:1, 2:1 or 1:1.

8. The preparation according to any one of the preceding claims, characterized in that the preparation comprises an essentially non-swellable and non-erosive diffusion matrix.

9. The preparation according to Claim 8, characterized in that the diffusion matrix contains at least ethylcellulose and at least one fatty alcohol as the constituents having an essential influence on the release behavior of the active ingredients.

10. The preparation according to Claim 8 or Claim 9, characterized in that the preparation does not comprise any relevant amount of alkaline and/or water-swellable substances, in particular acrylic acid derivatives and/or hydroxyalkyl celluloses.

11. The preparation according to any one of the preceding claims, characterized in that the preparation comprises the usual fillers and excipients, in particular lubricants, flow agents, plasticizers and the like.

12. The preparation according to Claim 11, characterized in that the lubricant is magnesium stearate, calcium stearate and/or calcium laurcate and/or fatty acids, especially preferably stearic acid.

13. The preparation according to Claim 11, characterized in that the flow agent is highly dispersed silica, especially preferably Aerosil®, talc, cornstarch, magnesium oxide, magnesium stearate and/or calcium stearate.

14. A storage stable pharmaceutical preparation comprising oxycodone and naloxone in an essentially non-swellable diffusion matrix, characterized in that the matrix is characterized by ethylcellulose and at least one fatty alcohol in its essential release properties and the preparation comprises oxycodone and naloxone in a weight ratio range from max. 25:1, preferably max. 20:1, 15:1, especially preferably 5:1, 4:1, 3:1, 2:1 or 1:1.

15. The preparation according to Claim 14, characterized in that oxycodone and/or naloxone is used in the form of its pharmaceutically acceptable and immediately active derivatives of same such as the free base, salts and the like.

16. The preparation according to Claim 15, characterized in that oxycodone and/or naloxone is in the form of the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

17. The preparation according to any one of Claims 14 through 16, characterized in that the oxycodone is present in excess based on the unit amount of naloxone.

18. The preparation according to any one of Claims 14 through 17, characterized in that naloxone is present in a quantity range from 1 to 50 mg.

19. The preparation according to any one of Claims 14 through 18, characterized in that oxycodone is present in a quantity range from 10 to 150 mg, preferably 10 to 80 mg.

20. The preparation according to any one of Claims 14 through 19, characterized in that the preparation comprises an essentially non-swellable and non-erosive diffusion matrix.

21. The preparation according to Claim 20, characterized in that the diffusion matrix contains at least ethylcellulose and at least one fatty alcohol as constituents having an essential influence on the release behavior of the active ingredients.

22. The preparation according to Claim 20 or 21, characterized in that the preparation does not contain nay relevant amounts of alkaline and/or water-swellable substances, in particular acrylic acid derivatives and/or hydroxyalkyl celluloses.

23. The preparation according to any one of Claims 14 through 22, characterized in that the fatty alcohols are lauryl, myrestyl, stearyl, cetostearyl, ceryl and/or cetyl alcohol, especially preferably stearyl alcohol.

24. The preparation according to any one of Claims 14 through 23, characterized in that the preparation comprises the usual fillers and excipients, in particular lubricants, flow agents, plasticizers and the like.

25. The preparation according to Claim 24, characterized in that the lubricant is magnesium stearate, calcium stearate and/or calcium laureate and/or fatty acids, especially preferably stearic acid.

26. The preparation according to Claim 24, characterized in that the flow agent is highly dispersed silica, especially preferably Aerosil®, talc, cornstarch, magnesium oxide, magnesium stearate and/or calcium stearate.

27. The preparation according to any one of the preceding claims, characterized in that instead of ethylcellulose, commercially available polymer mixtures containing ethylcellulose, preferably Surelease® E-7-7050 may be used.

28. The preparation according to any one of the preceding claims, characterized in that the preparation is formulated for oral, nasal, rectal administration or by inhalation.

29. The preparation according to any one of the preceding claims, characterized in that the preparation is a tablet, a pill, a capsule, granules and/or a powder.

30. The preparation according to any one of the preceding claims, characterized in that the preparation or precursors thereof is produced by buildup and/or breakdown granulation.

31. The preparation according to any one of the preceding claims, characterized in that the preparation or precursors thereof is produced by extrusion.

32. The preparation according to any one of the preceding claims, characterized in that the preparation is stable in storage for at least 2 years under standard conditions (60% relative humidity, 25°C) to conform to approval standards.

Fig 1

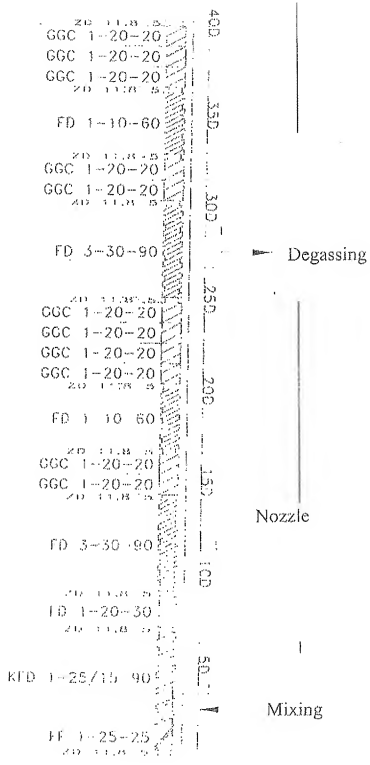

GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
FD 1-10-60
GGC 1-20-20
GGC 1-20-20
FD 3-30-90
GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
FD 1-10-60
GGC 1-20-20
GGC 1-20-20
FD 3-30-90
FD 1-20-30
KFD 1-25/15-90
FF 1-25-25
400
350
300
250
200
150
100
50
Degassing
Nozzle
Mixing

Fig 2

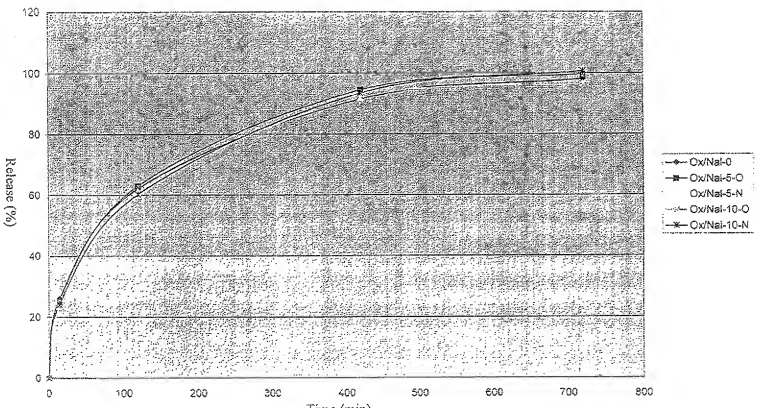

120
100
80
60
40
20
0
Release (%)
0
100
200
300
400
500
600
700
800
Time (min)
Ox/Nal-0
Ox/Nal-5-O
Ox/Nal-5-N
Ox/Nal-10-O
Ox/Nal-10-N

Fig 3A

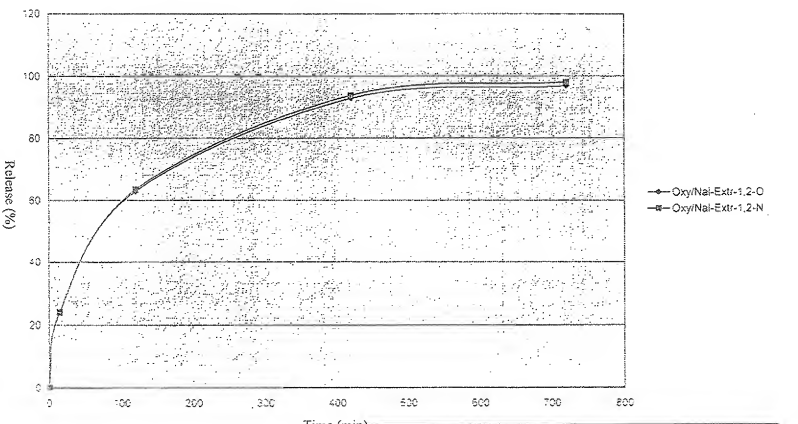

120
100
80
60
40
20
0
Release (%)
0
100
200
300
400
500
600
700
800
Time (min)
Oxy/Nal-Extr-1,2-O
Oxy/Nal-Extr-1,2-N

Fig 3B

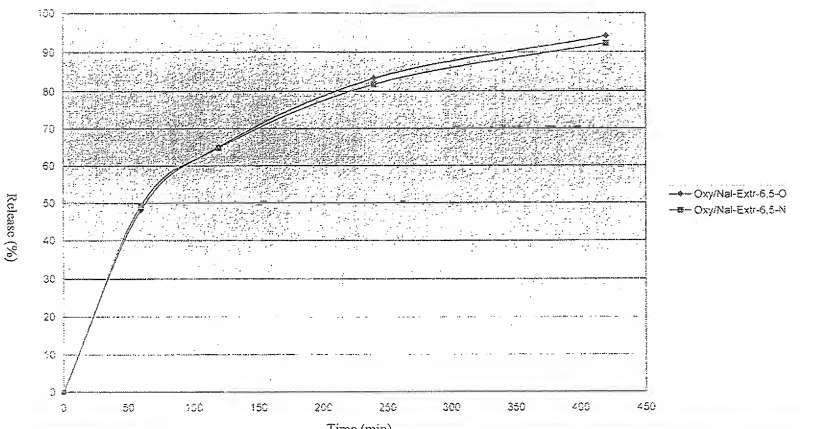

100
90
80
70
60
50
40
30
20
10
0
Release (%)
0
50
100
150
200
250
300
350
400
450
Time (min)
Oxy/Nal-Extr-6,5-O
Oxy/Nal-Extr-6,5-N

Fig 4A

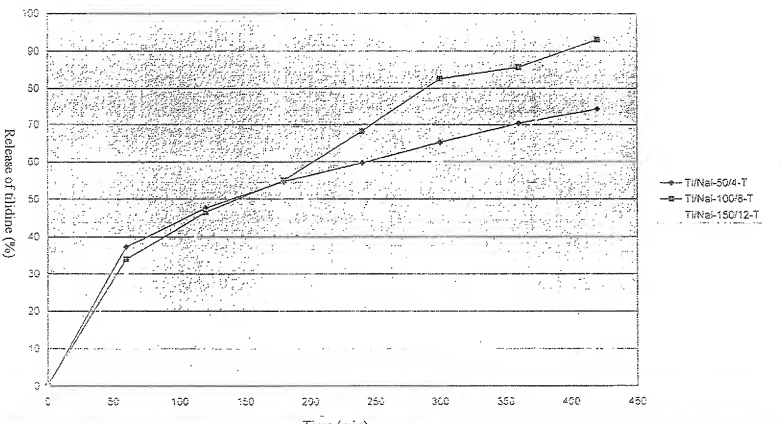
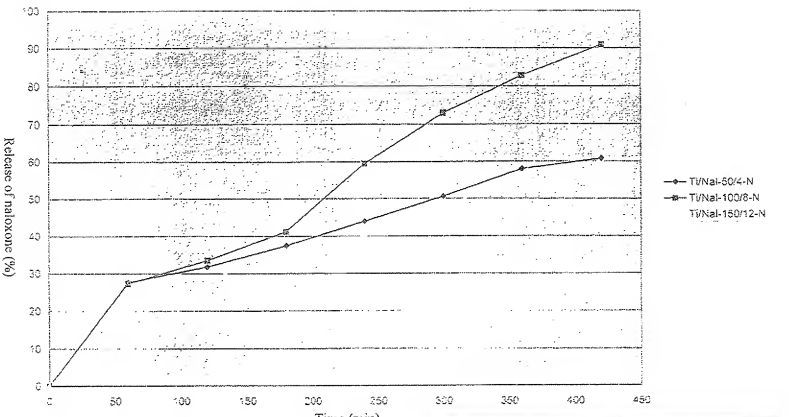

Release of tildine (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
Time (min)
Ti/Nsi-50/4-T
Ti/Nsi-100/8-T
Ti/Nsi-150/12-T

Fig 4B


Release of naloxone (%)
0
10
20
30
40
50
60
70
80
90
100
0
50
100
150
200
250
300
350
400
450
Time (min)
Ti/NaI-50/4-N
Ti/NaI-100/8-N
Ti/NaI-150/12-N

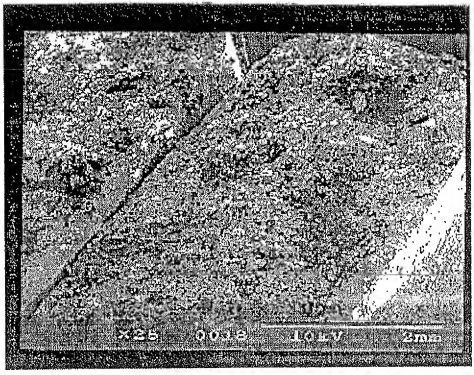


Fig 5A: Surface of the Ox/Nal-10 tablet, magnification 25X. Voltage 10 kV. Bar length 2 mm

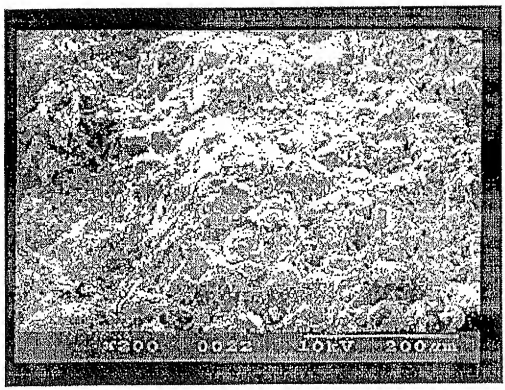


Fig 5B: Surface of the Ox/NaI-10 tablet, magnification 200X. Voltage 10 kV. Bar length 200 µm

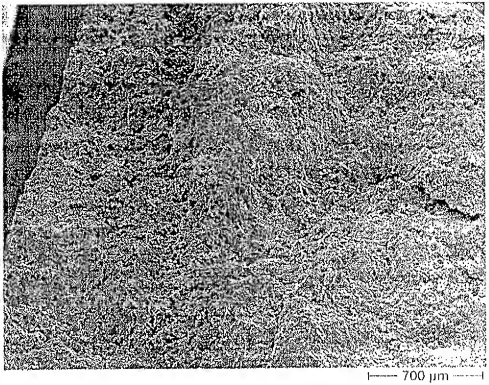


Fig 6A: Surface of the Ox/Nal extruded tablet, magnification 40X. Voltage 10 kV. Bar length 700 μm

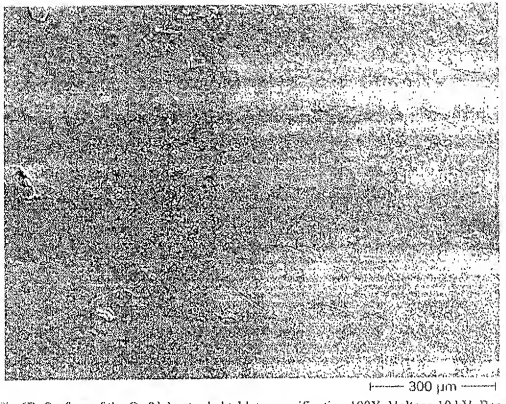


Fig 6B: Surface of the Ox/Nal extruded tablet, magnification 100X. Voltage 10 kV. Bar length 300 µm

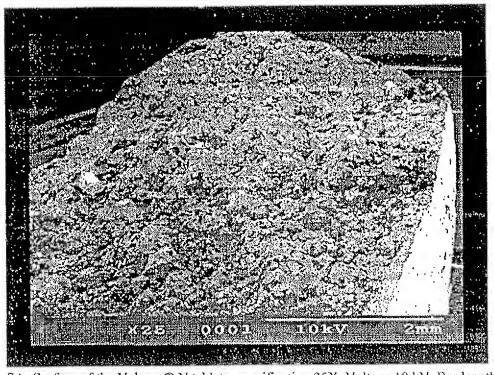


Fig 7A: Surface of the Valoron® N tablet, magnification 25X. Voltage 10 kV. Bar length 2 mm

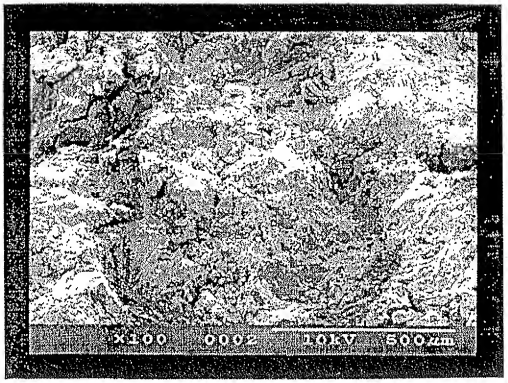


Fig 7B: Surface of the Valoron® N tablet, magnification 100X with crystal rose (filidine, lower left). Voltage 10 kV. Bar length 500 μm